Stress, depression and cognition across the life span

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CHAPTER 8

HYPOTHALAMIC-PITUITARY-ADRENAL AXIS ACTIVITY AND COGNITIVE FUNCTIONING IN OLDER ADULTS

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ABSTRACT

Objectives

Inconsistent results are found in the involvement of the Hypothalamus-Pituitary-Adrenal (HPA)-axis in cognitive functioning. This study examined the association between various saliva cortisol measures and cognitive functioning in older persons with and without a depressive disorder.

Methods

Cross-sectional data on 328 depressed and 119 non-depressed older adults between 60-93 years from the Netherlands Study of Depression in Older adults were used. 1-h awakening cortisol, evening cortisol, diurnal slope and cortisol suppression were measured in saliva. Cognitive functioning was evaluated by episodic memory, processing speed, interference control, and working memory. Multivariate analyses were adjusted for relevant confounders.

Results

No significant associations between cortisol and cognitive functioning were observed in the total sample. Total cortisol secretion over the first hour after awakening and worse episodic memory, and higher cortisol levels at awakening and better working memory were significantly associated in non-depressed, but not in depressed older adults.

Conclusions

Cortisol was not systematically associated with cognitive functioning in depressed older adults. The association between depression and cognitive dysfunctioning is likely the consequence of other biological or psychological mechanisms.

INTRODUCTION

Patterns of cognitive decline in older adults are highly variable and still not completely understood. To improve our knowledge about cognitive aging it is important to identify contributing factors, such as the stress hormone cortisol. Prolonged exposure to elevated cortisol levels might have an adverse effect on cognitive functioning because it can cross the blood-brain barrier, and binds to specific receptors mainly in the hippocampus, amygdala, and frontal lobes, which are important areas involved in learning, memory, and executive functioning (1). In community-based studies increases in cortisol were often associated with decreases in cognitive functioning (2-7), however, no association (8;9) or a positive association were also observed (3). In addition, in a community-based study Potvin et al. (10) observed that high morning cortisol was associated with an increased risk of cognitive impairment in highly depressed/anxious older adults and with a decreased risk in healthy older adults. This may suggest that the association between cortisol and cognitive functioning is different for depressed and non-depressed older adults. In non-depressed older adults most studies observed higher cortisol levels to be associated with poorer cognitive functioning (11-14), but the reversed association with higher cortisol associated with better cognitive performance has also been observed (15). Although cognitive dysfunctioning is often observed in depressed older persons (16), few studies examined the role of cortisol on cognitive functioning in late-life depression. In previous research from our study group higher morning cortisol and a less dynamic cortisol awakening response were associated with depression (17). These altered cortisol levels might also be related to cognitive dysfunctioning in late-life depression. However, two studies examining this association did not observe an association between daytime cortisol and cognitive functioning in depressed older persons (18;19), whereas another study observed higher post-dexamethasone levels to be associated with better memory performance (20).

Inconsistent findings on the association between cortisol and cognitive functioning might also be the result of methodological limitations and differences between studies. Sample sizes are often small and most studies are limited in the correction for confounding variables. In addition, many studies have obtained only one cortisol measure. However, different cortisol measures reflect various aspects of HPA-axis functioning and might be differentially associated with cognitive functioning. Morning cortisol reflects the natural response of the HPA-axis to awakening, while evening samples reflect the basal cortisol levels, and dexamethasone suppression, the negative feedback system of the HPA-axis. In this study the association between multiple cortisol measures and cognitive functioning are examined in a large sample of older adults. In addition it is examined if the association between cortisol and cognitive functioning is different for depressed and non-depressed older adults.

METHODS

Study sample

Data were derived from the baseline assessment (April 2007 to September 2010) of the Netherlands Study of Depression in Older Persons (NESDO). NESDO is a multi-site prospective cohort study of 510 older adults aged 60 through 93. People in different developmental and severity stages of psychopathology as well as controls with no psychiatric diagnosis participated. An extensive description of the population and methods of recruitment are described in detail elsewhere (21). In short, depressed older adults (n=378) were recruited from both mental health care institutes and general practices and were included when they fulfilled the DSM-IV criteria (22) for a 6-month diagnosis of major depression (95.0%), dysthymia (26.5%) or minor depression (5.0%). Non-depressed controls (n=132) were recruited from general practices and had no lifetime diagnosis of depression. Exclusion criteria were a primary clinical diagnosis of dementia, psychotic disorder, obsessive compulsive disorder, bipolar disorder, severe addiction disorder, a Mini Mental State Examination-score (MMSE) below 18 (out of 30 points), and insufficient command of the Dutch language. The study protocol was approved by the Ethical Review Board of the VU University Medical Center and written informed consent was obtained from each participant.

Persons with at least one cortisol measure were included in the analyses, which resulted in 447 respondents; 328 depressed and 119 non-depressed older adults. Excluded persons (n=63) did not differ in depressed state, sex, alcohol use, and smoking status from the included persons. However, the excluded persons had worse cognitive functioning, fewer years of education, and a higher age ($p<0.05$).

Measures

Depression diagnosis

The Composite International Diagnostic Interview (CIDI; WHO version 2.1; life-time version) was used to assess major depression and dysthymia according to DSM-IV-TR criteria. Additional questions were asked to determine the DSM-IV research diagnosis of minor depression. The CIDI is a structured clinical interview that is designed for use in research settings and has high validity for depressive disorders (23).

Salivary cortisol

As described in more detail elsewhere (17) respondents were instructed to collect saliva samples at home on two consecutive days shortly after the interview. Saliva samples were obtained at six time points; time of awakening (T1), 30 minutes (T2), 45 minutes (T3), and 60

minutes (T4) post-awakening and at 22:00 h (T5). In addition, dexamethasone suppression was measured by sampling the next morning at awakening (T6) after dexamethasone ingestion of 0.5 mg the night before (directly after T5).

The area under the curve with respect to the ground (AUCg) and with respect to the increase (AUCi) were computed (24). The AUCg reflects the total cortisol secretion over the first hour after awakening, the AUCi is calculated as follows: AUCg – the awakening sample * 1 hour, and emphasizes the changes in cortisol over the first hour after awakening, reflecting the dynamic of the cortisol awakening response (24;25). Diurnal slope was calculated by subtracting the evening level (T5) from the level at awakening (T1). The dexamethasone suppression ratio was calculated by dividing the cortisol value at awakening (T1) by the cortisol value at awakening the day after dexamethasone ingestion (T6).

Cognitive functioning

Four domains of cognitive functioning were included; episodic memory, processing speed, interference control and working memory. A previous study conducted a factor analysis on separate cognitive tasks and showed primary loadings on these cognitive domains (26). Z-scores from the separate cognitive tasks were calculated, and the mean z-scores of the cognitive tasks representing one cognitive domain were used.

Episodic memory consisted of direct and delayed recall of the 10-Word test, a modified version of the auditory verbal learning test (27). In five trials the respondent had to recall as many words as possible and after a distraction period of 20 minutes the respondent was asked to name again the words learned before. Processing speed was assessed with the first two cards of the abbreviated version of the Stroop colour-Word test (28), and interference control consisted of the interference score of the Stroop colour-Word test (29). Working memory was assessed with the subtest digit span from the Wechsler Adult Intelligence Scale (30). Both the number of correct digits forwards and backwards were used as measure of working memory.

Covariates

Several variables associated with HPA-axis functioning and cognitive functioning were selected as covariates a priori (age, sex, education, diabetes mellitus, body mass index (BMI), smoking status, alcohol use, time of awakening, season, and sleep duration). In previous research from our study group (17) these variables were consistently associated with various cortisol measures. Information about age, sex, and year of education was collected. The presence of diabetes mellitus was assessed by self-report and BMI (kg/length^2) was measured. Smoking status was dichotomized into 'non-smoker' and 'current smoker' and alcohol use was categorized into 0 drinks per day, more than 0 and less than 2 drinks per day, and 2 or more

drinks per day. Time of awakening was assessed on the first cortisol sampling day, and season was dichotomized into seasons with less daylight (October-February) and more daylight (March-September), average sleep duration was dichotomized into ≤6 hours per night versus >6 hours per night.

Statistical analyses

To examine the association between cortisol and cognitive functioning, linear regression analyses were performed, with the cortisol measures (morning cortisol, AUCg, AUCi, evening cortisol, diurnal slope, dexamethasone suppression ratio) as independent variables and the cognitive domains (episodic memory, processing speed, interference control, working memory) as dependent variables adjusted for covariates. In addition, to observe if the association between cortisol and cognitive functioning was different for depressed and non-depressed older adults, linear regression analyses were performed including the interaction term between the cortisol measure and depressed state (yes/no) to the fully adjusted models. When significant interaction terms ($p<0.10$) were observed stratified analyses were performed.

RESULTS

Table 1 shows the characteristics of the study sample. Depressed older adults did not differ in age and sex, but had fewer years of education compared to non-depressed controls. On all domains of cognitive functioning, scores were lower in depressed compared to non-depressed persons.

Table 2 shows the results of the adjusted linear regression analyses of the association between several cortisol measures and cognitive functioning. No significant associations were observed between cortisol and cognitive functioning in the total sample. Only two out of 24 interaction terms between cortisol and depressed state were significant; AUCg and episodic memory (B=0.03, p=0.04) and morning cortisol and working memory (B=-0.02, p=0.09). Stratified analyses showed significant associations only in non-depressed older adults; a higher AUCg was associated with worse episodic memory (B=-0.023; 95%-CI=-0.044;-0.001) and a higher morning cortisol with better working memory (B=0.021; 95%-CI=0.003;0.038). Since two significant interaction effects can be expected on the basis of chance only, the overall results do not confirm an important, consistent association between cortisol indicators and cognitive functioning.

Table 1. Characteristics of the study population.

	Total sample N=447	Non-depressed N=119 (26.6%)	Depressed N=328 (73.4%)	X^2/ t/ U (df) p
Socio-demographics				
Female, n (%)	284 (63.5)	73 (61.3)	211 (64.3)	0.34 (1) .56
Age, mean (SD)	70.2 (7.2)	69.7 (7.1)	70.4 (7.2)	-0.98 (445) 0.33
Years of education, mean (SD)	11.1 (3.6)	12.7 (3.4)	10.5 (3.6)	5.8 (445) <.001
Cognitive functioning				
Immediate recall, mean (SD)	32.8 (6.9)	35.0 (6.1)	32.0 (7.0)	4.18 (236) <.001
Delayed recall, mean (SD)	6.2 (2.2)	6.7 (2.0)	6.0 (2.2)	3.10 (232) .001
Stroop I, median (IQR)	19.0 (4)	18.0 (3.0)	20.0 (5.3)	14173.0<.001
Stroop II, median (IQR)	25.0 (6)	23.0 (6)	25.0 (7.0)	12951.0<.001
Digit span forwards, mean (SD)	8.2 (1.8)	8.5 (1.8)	8.1 (1.8)	2.34 (436) .020
Digit span backwards, mean (SD)	5.4 (1.8)	5.7 (1.7)	5.3 (1.9)	2.49 (436) .013
Stroop interference, median (IQR)	1.13 (0.7)	0.91 (0.56)	1.19 (0.59)	12742.5<.001
Cortisol				
Morning cortisol, mean (SD) (n=429)	18.1 (10.2)	17.1 (8.96)	18.8 (10.6)	-1.26 (427) 0.21
AUCg, mean (SD) (n=388)	19.7 (9.1)	19.1 (7.6)	19.9 (9.6)	-0.74 (386) 0.46
AUCi, mean (SD) (n=388)	1.28 (8.6)	2.12 (8.4)	0.96 (8.6)	1.19 (386) 0.24
Evening cortisol, mean (SD) (n=432)	5.3 (5.8)	5.09 (5.74)	5.41 (5.87)	-0.52 (430) 0.60
Diurnal slope, mean (SD) (n=416)	13.2 (10.5)	12.5 (9.6)	13.5 (10.84)	-0.84 (414) 0.40
Cortisol suppression ratio, mean (SD) (n=361)	3.1 (2.4)	3.10 (2.70)	3.16 (2.22)	-0.19 (359) 0.85
Health and Lifestyle characteristics				
Diabetes mellitus, n (%)	50 (11.2)	16 (13.4)	34 (10.4)	0.81 (1) .37
BMI, mean (SD)	26.6 (4.3)	27.0 (4.0)	26.4 (4.4)	1.36 (444) .18
Smoking, n (%)	93 (20.9)	9 (7.6)	84 (25.7)	17.4 (1) <.001
No alcohol use, n (%)	141 (32.0)	15 (12.9)	126 (38.9)	26.4 (1) <0.001
>0 and <2 drinks per day, n (%)	248 (56.4)	76 (65.5)	172 (53.1)	Ref
≥2 drinks per day, n (%)	51 (11.6)	25 (21.6)	26 (8.0)	15.3 (1) <0.001
Sampling factors				
Time of awakening, mean (SD)	7:46 (1.0)	7:43 (0.9)	7:47 (1.1)	-0.41 (254) 0.68
More daylight, n (%)	289 (68.2)	85 (76.7)	204 (65.2)	4.9 (1) .03
More than 6 hrs of sleep, n (%)	300 (67.7)	102 (87.2)	198 (60.7)	27.5 (1) <.001

Abbreviations: AUCg, area under the morning curve with respect to the ground; AUCi, area under the morning curve with respect to the increase; BMI, body mass index.

DISCUSSION

In this large cohort study of older adults no significant associations were observed between multiple cortisol measures and memory, processing speed and executive functioning. In addition, these associations were not substantially different for between depressed and non-depressed older adults.

Our study sample consisted of a high percentage of depressed persons, therefore the results in the total group are mainly driven by the depressed older adults. In the depressed

Table 2. Association between cortisol measures and cognitive functioning in older adults (n=447).

	Episodic memory	Processing speed	Interference control	Working memory
Adjusted models	B (95%-CI)	B (95%-CI)	B (95%-CI)	B (95%-CI)
Morning cortisol	0.002 (-0.006;0.010)	0.007 (-0.002;0.015)	-0.002 (-0.011;0.007)	0.004 (-0.004;0.012)
AUCg	-0.002 (-0.012;0.007)	-0.002 (-0.012;0.008)	-0.002 (-0.013;0.009)	0.002 (-0.008;0.011)
AUCi	-0.003 (-0.014;0.007)	-0.009 (-0.020;0.001)	0.000 (-0.011;0.012)	-0.003 (-0.013;0.007)
Evening cortisol	-0.007 (-0.022;0.007)	-0.007 (-0.021;0.008)	0.000 (-0.016;0.017)	-0.009 (-0.023;0.005)
Diurnal slope	0.002 (-0.005;0.010)	0.006 (-0.002;0.014)	-0.002 (-0.011;0.008)	0.005 (-0.002;0.013)
Cortisol suppression ratio	-0.024 (-0.063;0.014)	0.000 (-0.039;0.039)	-0.010 (-0.053;0.034)	-0.002 (-0.040;0.036)
Interaction cortisol* depressed (yes/no)	B, p	B, p	B, p	B, p
Morning cortisol*depressed	0.01 (0.35)	-0.02 (0.15)	0.02 (0.16)	-0.02 (0.09)
AUCg*depressed	0.03 (0.043)	-0.001 (0.93)	-0.02 (0.16)	-0.01 (0.38)
AUCi*depressed	0.01 (0.51)	0.02 (0.15)	-0.01 (0.50)	0.01 (0.35)
Evening cortisol* depressed	-0.014 (0.42)	0.002 (0.90)	0.03 (0.12)	-0.02 (0.36)
Diurnal slope*depressed	0.01 (0.31)	-0.02 (0.11)	0.01 (0.48)	-0.02 (0.12)
Cortisol suppression ratio*depressed	0.05 (0.21)	-0.06 (0.11)	-0.04 (0.36)	-0.05 (0.25)

Abbreviations: AUCg, area under the morning curve with respect to the ground; AUCi, area under the morning curve with respect to the increase.
Adjusted for age, sex, education, smoking, alcohol use, body mass index, diabetes mellitus, time of awakening, hours of sleep, and daylight.

group only, no associations between any of the cortisol measures and cognition were found (data not shown), which confirms this conclusion. Our findings suggest that a glucocorticoid cascade hypothesis (31) whereby stress-related cortisol levels lead to cognitive impairments might not be substantial in depressed older adults. In previous research from our study group, higher morning cortisol was associated with depressed state (17). We also showed earlier that depression and anxiety (severity) was consistently associated with worse memory, processing speed, and executive functioning (26). However, because we did not find an association between cortisol and cognitive functioning, higher cortisol levels do not seem to be an explanation for worse cognitive functioning in depressed older adults. A high symptom load of current depressive symptoms but also comorbid anxiety might be more important in the association with cognitive dysfunctioning in late-life depression. In addition, other mechanisms might be important, such as vascular and inflammatory processes (32). Studies in depressed older adults observed white matter hyperintensities and reductions in hippocampus volume to be associated with cognitive impairments, whereas cortisol levels did not. This suggests that vascular factors leading to brain changes might be more important with respect to cognitive dysfunctioning in late-life depression than HPA-axis functioning (18;19).

Compared to depressed older adults morning cortisol and AUCg were significantly associated with respectively better working memory and poorer episodic memory in non-depressed

older adults. Higher morning cortisol and better memory performance was also observed in previous research (15). However, as these were the only significant differences out of 24 tests, these results may be findings by chance, and no firm conclusions can be stated about a stronger association between cortisol and cognitive functioning in non-depressed older adults compared to depressed older adults.

Strengths of our study are that we examined a wide range of cortisol measures, reflecting the diurnal rhythm of cortisol, and different cognitive domains were assessed. In addition, a large sample was included and we were able to adjust for relevant confounders. We expect that our findings were not the result of unreliability of the cortisol measures. In previous research from our study group (17), several variables that are expected to be associated with cortisol (diabetes mellitus, body mass index, smoking status, time of awakening, depression severity) were indeed associated with various cortisol measures, suggesting that the cortisol measures used were valid and reliable. A limitation of our study is that the cortisol measures did not reflect cortisol exposure over several years. It might be expected that especially chronically elevated levels of cortisol might impact on cognitive functioning via the glucocorticoid cascade hypothesis. Further studies are required to examine this hypothesis.

In conclusion, our findings suggest that cortisol is not likely to be a major factor contributing to poorer cognitive functioning in depressed older adults.

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